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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,712	03/30/2001	Gregor Sagner	5443	7485

22829 7590 01/21/2003

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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	13

DATE MAILED: 01/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/823,712	Applicant(s) SAgner
	Examiner Arun Chakrabarti	Art Unit 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 4, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14, 17-22, and 28-37* is/are rejected.

7) ☒ Claim(s) *15, 16, and 23-27* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Continued Examination Under 37 CAR 1.114

1. A request for continued examination under 37 CAR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CAR 1.114, and the fee set forth in 37 CAR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CAR 1.114. Applicant's submission filed on December 4, 2002 has been entered.

Specification

2. Claims 1-3, 7-10, 12, 13 and 17 have been amended and new claims 18-37 have been added.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 31-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 31-37 are rejected over the recitation of the negative limitations "but need not be." in claim 31, last line of section (f). (See MPEP 2173.05 (I)) -- "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli,* USPQ 393 (Bd. App. 1983), *aff'd mem.,* 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement". In the instant application, negative limitations inserted in the amended claims do not have any expressed basis in the original specification (as described in paragraphs 188-221 of U.S. Publication NO; 2002/0058262 A1).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1-30 are rejected under 35 U.S.C. 103(a) over Wittwer et al. (U.S. Patent 6,232,079 B1) (May 15, 2001) in view of Brown et al. (U.S. Patent 6,143, 496) (November 7, 2000).

Wittwer et al teach a method for determining the efficiency of the amplification ("Note that the amplification efficiency of the CTFR fragment appears greater than the neu fragment. The amolification efficiency can be rigorously determined by integrating the melting peak data as in example 16 (Column 41, last two sentences of the fourth paragraph)"of a target nucleic acid (Abstract, Column 13, line 65 to Column 14, line 32, and Figure 44 and Examples 7, 8, and 16) comprising the steps of:

b) the target nucleic acid is amplified under defined reaction conditions and the amplification is measured in real-time (Figure 44);

c) a defined signal threshold value is set (Figure 44);

d) determining the cycle number for each dilution at which the signal threshold value is exceeded (Figure 44 and Examples 7, 8, and 16));

e) determining a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded (inherently taught in Figures 15-17 and 42 and Column 33, line 10 to Column 34, line 52); and

f) calculating the amplification efficiency from the function determined in step e) (Figure 44 and Examples 7, 8, and 16).

Wittwer et al teach a method, wherein the amplification efficiency of a certain original amount of target nucleic acid is determined as the negative and reciprocal local first derivative of the continuously differentiable function (Figure 16 and Examples 7, 8, and 16).

Wittwer et al also teach a method for the absolute quantification of a target nucleic acid in a sample (Abstract and Column 12, line 43 to Column 13, line 64) comprising the steps of:

a) determination of the amplification efficiencies of the target nucleic acid and of an internal or external standard (Abstract and Example 16);

b) amplification of the target nucleic acid contained in the sample and of the standard under the same defined reaction conditions (Abstract and Example 16 and Figure 44);

c) measurement of the amplification of the target nucleic acid and standard in real time (Figure 44);

d) calculation of the original copy number in the sample with the aid of amplification efficiencies determined in step a) (Example 16 and Column 13, lines 29-45).

Wittwer et al. also teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from SybreGreen I (Example 14).

Wittwer et al. teach correction of copy number with the aid of amplification efficiencies (Example 16).

Wittwer et al inherently teach calculating the quotients of the function values (copy number) from the target nucleic acid and reference nucleic acid for the sample to be analyzed as well as for the calibrator sample and determination of the ratio of the two quotients as a measure for the original amount of target nucleic acid contained in the sample (Example 16 and Column 8, line 40 to Column 9, line 19).

Wittwer et al do not teach the preparation of different dilutions of the target nucleic acid.

Brown et al teach the preparation of a dilution of the target nucleic acid (Abstract, Example 1, Table 1 and Figure 8);

Wittwer et al do not teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from TaqMan probes.

Brown et al teach a method, wherein the amplified nucleic acids are detected with the aid of at least one fluorescent-labeled hybridization probe selected from TaqMan probes (Column 3, lines 25-59).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. since Brown et al state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state, "Thus, with

rapid cycling the required times for amplification are reduced approximately 10-fold, and specificity is improved (Column 21, lines 1-3)". An ordinary practitioner would have been motivated to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. in order to achieve the express advantages , as noted by Wittwer et al., of a method that allows rapid cycling by which the required times for amplification are reduced approximately 10-fold, and specificity is improved and also to achieve the express advantages, as noted by Brown et al., of a method for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process .

Allowable Subject Matter

7. Claims 15, 16, and 23-27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Amendment

8. In response to amendment, previous 103(a) rejection has been withdrawn. However, a 112 (first paragraph) rejection and a new 103 (a) rejection have been included.

Response to Arguments

9. Applicant's arguments filed on December 4, 2002 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant argues that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Brown et al as Brown et al. state, "A need also exists for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process (Column 4, lines 23-26)". Moreover, Wittwer et al. state,"Thus, with rapid cycling the required times for amplification are reduced approximately 10-fold, and specificity is improved (Column 21, lines 1-3)". An ordinary practitioner would have been motivated to substitute and combine the preparation of a dilution of the target nucleic acid and fluorescent-labeled hybridization probe selected from TaqMan probes of Brown et al in the method of sampling, amplifying and quantifying segment of nucleic acid of Wittwer et al. in order to achieve the express advantages , as noted by Wittwer et al., of a method that allows rapid cycling by which the required times for amplification are reduced approximately 10-fold, and specificity is improved and also to achieve the express advantages, as noted by

Brown et al., of a method for performing multiple different amplification and detection reactions in parallel on a single specimen and for economizing usage of reagents in the process.

Applicant also argues that Wittwer reference does not teach the main feature of the instant invention which is the determination of an amplification efficiency. This argument is moot in view of the new ground of rejection based on new prior art Wittwer et al. (U.S. Patent 6,232,079 B1) (May 15, 2001) which clearly teaches amplification efficiency determination as specified above ("Note that the amplification efficiency of the CTFR fragment appears greater than the neu fragment. The amolification efficiency can be rigorously determined by integrating the melting peak data as in example 16 (Column 41, last two sentences of the fourth paragraph)".

Applicant also argues that Wittwer reference does not teach the determination of a non-linear continuously differentiable function of a logarithm of copy number of target nucleic acid used for the amplification as a function of the cycle number at which the signal threshold value is exceeded. This argument is also moot in view of the new ground of rejection based on new prior art.

Applicant then argues the 103 rejection is improper because it is obvious to try and lacks a reasonable expectation of success.

With regard to the " lacks a reasonable expectation of success. " argument, The MPEP 2143.02 states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ

143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Wittwer reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different biological samples were actually experimentally amplified and found to be functional (Examples 7, 8 and 16). This evidence of functionality trumps the attorney arguments, which argues that

Wittwer reference is an invitation to research, since Wittwer steps beyond research and shows the functional product.

In view of the response to argument, all 103 (a) rejections are hereby being properly maintained.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Chakrabarti

Patent Examiner

Art Unit 1634

JEFFREY FREDMAN
PRIMARY EXAMINER